REVIEW

Potential role of dendritic cells for progression of atherosclerotic lesions

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Atherosclerosis is a lipid related chronic inflammatory disease in which immune mechanisms play a pivotal part. Its lesion is filled with large numbers of immune cells. In 1995 dendritic cells (DCs) were identified in atherosclerotic plaques and thought to play an important part in atherogenesis. DCs express MHCI and II, HLA-DR, CD1a, ICAM-1 and VCAM1 on their surfaces, and this explains their unique ability to activate naive T cells. The risk factors for atherosclerosis are the factors for DCs' activation and migration. Mature DCs are capable of presenting antigen to T cells, which play an important part in progression of disease. Statin and diltiazem have been shown to protect endothelial function by suppressing the function of DCs and play an important part in preventing atherosclerosis.

Atherosclerosis is a lipid related chronic inflammatory disease of the vessel wall that affects various vascular beds.[1] Its pathogenesis involves inflammatory cells, systemic markers, and proinflammatory signalling systems. It is well established that atherosclerotic plaques contain immune competent cells, among which monocytes derived macrophages and T lymphocytes are the most conspicuous. Extensive evidence supports an inflammatory/immune activation of plaques as a cause of acute coronary syndromes. Being a professional antigen presenting cell, dendritic cells (DCs) may play an important part in this activation and may affect in the start and progression of atherosclerosis. Recently we reported that the function of DCs is increased in patients with unstable angina and the activated function of DCs is an important mediator in the inflammatory process leading to plaque instability and vulnerability towards rupture.[2]

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IMMUNE CELLS IN THE ATHEROSCLEROTIC LESION

Macrophages and T cells are common components of atherosclerotic lesion, which also may contain mast cells and DCs.[3] Macrophages are seen in all stages of atherosclerosis.[4] The degree of macrophages infiltration has been shown to distinguish between unstable and stable coronary lesion.[5] T cells represent the other main cell of atherosclerotic lesions. T cells of both the helper (CD4+) and (CD8+) types have been detected in human atheroma and have been shown to be immunologically activated.[6] The first direct evidence for this activation was the demonstration of human leucocyte antigen (HLA-DR) expression on the surface of smooth muscle cells adjacent to the T lymphocytes in the lesions. This human lymphocyte antigen (HLA) expression is induced by interferon gamma (INF gamma), a product of activated T cells.[7] The presence of activated T lymphocytes in the atherosclerotic plaque suggests a local immune response, and it has been postulated that such a response may be directed against local antigens in the plaque. Immunohistochemical analysis has shown that T cells obtained by directional coronary atherectomy of culprit lesion in patients with acute coronary syndromes showed an increase in the expression of the interleukin 2 (IL2) receptors (CD25) compared with T cells obtained from so called stable lesions.[8]

Studies during the past decade have identified DCs in atherosclerotic plaques. DCs are present in their immature forms in the arterial wall and become activated during atherogenesis.[9 10] Atherosclerosis begins in youth and an accumulation of activated T lymphocytes, DCs, macrophages, and aberrant major histocompatibility complex (MHC) class expression on cells can be noticed in the intima predisposed to the development of atherosclerotic lesion later in life particularly if classic risk factors are present.[11] In atherosclerotic lesion more than 90% of DCs colocalising with T cells are located in the neovascularisation areas associated with inflammatory infiltrates.[12] DCs are present in the intima of arteries but not in veins of healthy humans and rabbits and these DCs accumulated most densely in those arterial regions that are subjected to major homodynamic stress by turbulent flow conditions and are known to predispose for the later development of atherosclerosis.[13] DCs are found in aortic atherosclerotic lesion in rats with diet induced hypercholesterolaemia[14] and also DCs infiltrate atherosclerotic lesion in apolipoprotein E deficient mice.[15] S-100 positive DCs were found in different types of atherosclerotic lesion and are thought to be essential for the stimulation and activation of T cells.[9] These findings suggest that DCs might be involved in atherosclerosis.

Abbreviations: DC, dendritic cell; INF gamma, interferon gamma; MHC, major histocompatibility complex; VCAM1, vascular cell adhesion molecule 1; ICAM1, intercellular adhesion molecule 1; EC, endothelial cell; TNF, tissue necrosis factor; HLA, human lymphocyte antigen

DCs AND THEIR FUNCTIONS

DCs, originally described by Steinman and Cohn in 1973, play a crucial part in the start of an immune response. They are the key antigen presenting cells and play crucial parts in the enhancement and regulation of cell mediated immune reactions.[16] DCs arise from a common CD34+ progenitor in the bone morrow and constitute a family of cells able to induced primary immune responses.[17] Their precursors exit the bone marrow and migrate via the blood stream to take up residence in different peripheral tissue to activate T cells. DCs express high levels of both class l and class 2 MHC molecules, HLA-DR, CDIa, and costimulatory molecules and this explains their unique ability to activate naive T cells. The presence of cell adhesion molecules such as intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1) on DC surfaces implies that DCs are capable of forming contacts responsible for T cell activation, as VACM1/very late antigen 4 (VLA4) and ICAM1/leucocyte function associated 1 (LAF1) are critical for T cell activation.[12] DCs also display on their surfaces CD1a, which has recently been recognised as an antigen presenting molecule in the same sense as the classic MHC1 and 2 molecules.[18] The capacity of DCs to stimulate T cells depends on their stage of maturation: after DCs have picked up antigens at their immature phagocytic stage, DC move to the regional lymphatic node while undergoing maturation.[17] Maturation boosts their capacity to efficiently present antigens to T cells and is mediated by upregulation of costimulatory molecules such as CD86 and CD40. Costimulation by the ligands CD80/CD86 and its receptors CD28 on T cells is required for efficient T cells stimulation.[19]

RECRUITMENT OF DCs TO THE VESSEL WALL

Changed endothelial function has a significant impact on DCs adherence to the endothelium. Endothelial cells (ECs) exposed to oxLDL, tissue necrosis factor α (TNFα), hypoxia, and infection are much more vulnerable to DCs attachment and transmigration than are non-activated ECs. EC apoptosis considerably increased DCs adhesion.[20] Endothelial activation increases the expression of adhesion molecules such as CD11/CD18, P selectin, E selectin, VACM1, and ICAM1.[21] E and P selectins mediate initial process of endothelial DCs rolling.[22] The initial contact is followed by the development of a more firm adhesion between DCs and ECs that is fascinated by CC-chemokines, lymphocyte function associated antigen (LFA1), CD11b, ICAM-2, and its ligand the DC specific C type lectin DC-SIGN.[23]

DCs AND THEIR EFFECT ON ATHEROSCLEROSIS

DCs adhesion and migration can be increased by endothelial activation and it has been shown that DCs interaction with ECs is strongly increased after blocking endothelial NO syntheses activity by using the endogenous NO syntheses inhibitor asymmetric dimethyl L-arginine (ADMA).[20] These results support the concept that endothelial activation accelerates DC mediated immune activation, finally leading to increased vascular inflammation. Nicotine activates DCs and augments their capacity to stimulate T cells proliferation and cytokine secration.[24] These effects of nicotine may be a contributory influence on the progression of atherosclerotic lesion. Bobryshev *et al*[25] reported that in advanced atherosclerotic lesion several cell types, including monocytes, macrophages, DCs, and smooth muscle cells overexpressed HSP70. DCs that overexpressed HSP70 frequently contacted T cells and also expressed HLA-DR. In early intimal lesion, HSP70 is overexpressed exclusively by DCs, which suggests that DCs might be involved in the early phase of atherogenesis. Oxidised LDL is one of the endogenous activators of immune response. In vitro studies show that increased concentrations of ox-LDL would favour a rapid generation of mature DCs from monocytes.[26] Autoantibodies to ox-LDL are considered to have a protective role in atherogenesis. In an experimental model in which an animal was immunised with ox-LDL, induction of atherosclerosis was not possible.[27] Ox-LDL induces a balanced immunogenic cascade. They showed that mildly oxidised LDL activated maturation of DCs and increased DC induced T cell activation and proliferation. However, high concentration of ox-LDL inhibited DC function because of increased DC apoptosis.[28]

Mature DCs are capable of processing and presenting antigen to T cell. Recently, T cells activation in atherosclerotic plaques has been attributed to DCs, as the presence of large number of DCs in atherosclerotic plaques and DCs can physically cluster with T cells, which is thought to be essential for stimulation and activation of T cells.[29] Antigen presenting DC induced T cells activation results in inflammatory amplification through T cells secretion of cytokines, including IFN gamma and TNFα and TNFβ. INF gamma released from T cells not only primes macrophages for activation but plays an important part in destabilising atherosclerotic plaques by inhibiting the proliferation of smooth muscle cells and decreasing their synthesis.[29] TNFα and IL1 also affect SMC proliferation. They stimulate further activation of macrophages induced secretion of matrix metalloproteinase-9 and promote expression of leucocytes adhesion molecules.[30]

CLINICAL SIGNIFICANCE

Several studies have shown that changes in endothelial function have a significant impact on DC maturation and DC recruitment to the endothelium may play an important part in atherosclerosis. Inhibition of DC-EC interaction may have an application in reducing the progression of cardiovascular disease. The population of DCs is heterogenous. There are lymphoid and myeloid pathways for the CD 34+DCs precursor to develop into DCs. Recent data suggest that myeloid DCs are required for T cells activation while lymphoid DCs induce T cells tolerance. Suppression of the myeloid subset of DCs and activation of the lymphoid subset may lead to new therapeutic avenues to regulate immunoreaction in atherosclerosis. Mainly two drugs from cardiovascular medicine were used to evaluate there function on DCs maturation and it was found that statin and diltiazem suppress the maturation of DCs. Weis *et al* showed that physiological concentration of HMG-CoA reductase (statin) decreases DC adhesion and transmigration.[20] Statins increase endothelial NO bioactivity, decrease endothelial apoptosis, and inhibit smooth muscle cell proliferation.[31] The result of this study suggests that by preserving endothelial function statins diminish inflammatory activity in the earlier phase of atherosclerosis. Recently Dazhu *et al* have proved that anti-inflammatory effects of atorvastatin in unstable angina patients may be attributed to its inhibition on DCs.[32] Bachetoni *et al* reported that diltiazem decreases DC dependent T cells activation and plays an important part in preventing atherosclerosis.[33] Diltiazem induced DCs have an impaired responsiveness to lipopolysaccharide and CD40 ligand because they produce decreased levels of IL12 and show a reduced ability to stimulate alloreactive T cell responses.

CONCLUSION

Atherosclerosis is an immunoinflammatory disease. Endothelial dysfunction and injury are the basis of onset of the atherosclerotic process. Endothelial adhesion and migration of DCs is increased by stimuli known to accelerate atherosclerosis. Such factors are viral and bacterial antigens, oxLDL, HSP, hypoxia, and changed NO synthesis activity of

endothelium. DC induced T cells activation followed by cytokines production contributes to coronary plaque instability and vulnerability towards rupture. Statin and diltiazem have been shown to protect endothelial function by inhibition of DC-EC interaction and have an application in reducing the progression of cardiovascular disease.

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